Mukaiyama Aldol−Prins Cyclization Cascade Reaction: A Formal Total Synthesis of Leucascandrolide A

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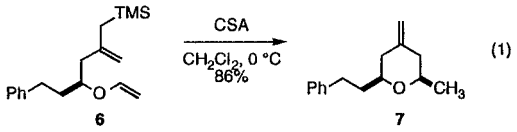
Cascade reactions, in which the reactive intermediate from one step directly undergoes further transformations, are important in organic synthesis because they can build up molecular complexity very rapidly.[1] We have developed a new cascade reaction, a Mukaiyama aldol coupling followed by a Prins cyclization,[2] and illustrate the potential of this new reaction with a synthesis of the leucascandrolide A macrolide.

Electrophilic additions to alkyl enol ethers are often problematic because the intermediate oxocarbenium ion, for example, **3**, is a very reactive electrophile and can react with the starting enol ether to produce oligomers, Figure 1. We sought to avoid this side reaction by introducing a nucleophile into the enol ether that would trap the oxocarbenium ion, for example, **4**, and produce a new ring. Where the internal nucleophile is an alkene, the trapping reaction becomes a Prins cyclization. The alkene must be reactive enough to prevent polymerization of the enol ether.

Initial studies with terminal alkenes as intramolecular nucleophiles only partially suppressed the competing polymerization reactions.[3] The use of a more reactive alkene, the allylsilane **6**, completely eliminated polymerization. The cyclization of **6** can be promoted by a variety of electrophiles, including a proton, eq 1. Aldehyde electrophiles reacted with enol **6** in the presence of a Lewis acid, but protonation and cyclization was competitive. The protonation reaction was suppressed by the addition of 2,6-di-*tert*-butylpyridine.



The aldol−Prins reactions of enol allylsilanes with a variety of aldehydes are listed in Table 1.[4] The yields ranged from good to excellent, and the *cis*-2,6-disubstituted tetrahydropyran products were formed stereoselectively. The aldol−Prins reaction worked well with aliphatic, aromatic, α,β-unsaturated, and oxygen-substituted aldehydes. The facial selectivity in the addition to the aldehyde, however, was minimal, as might be expected considering the distance between the reactive end of the enol and the stereogenic center in **6** and **21**. The advantage of this minimal facial selectivity is that there is no mismatched case when using other elements to control the aldehyde selectivity. Two obvious methods for introducing facial selectivity in the aldehyde component are the use of a chiral Lewis acid and the use of a chiral aldehyde. We develop the latter strategy in an approach to the natural product leucascandrolide A.

Leucascandrolide A was isolated from the sponge *Leucascandra caveolata* in 1996 and shows potent cytotoxicity against P388

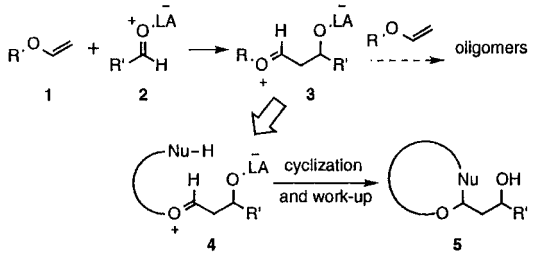
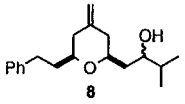
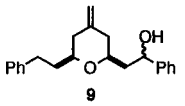
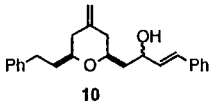
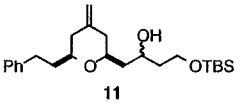
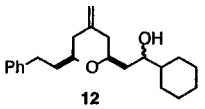
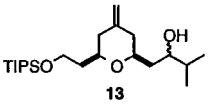


Figure 1. Conceptualization of the aldol−Prins reaction to avoid oligomerization in the reaction of electrophiles with alkyl enol ethers.

Table 1. Aldol−Prins Cyclizations with Simple Aldehydes[a]

Enol	Aldehyde	Yield[b]	Epimer Ratio[c]	Product
6	CHO	98%	1:1	 **8**
6	PhCHO	84%	1.2:1	 **9**
6	Ph CHO	87%	1.4:1	 **10**
6	TBSO CHO	87%	1.8:1	 **11**
6	CHO	72%	1.7:1	 **12**
21[d]	CHO	72%	1.1:1	 **13**

[a] Aldol-Prins cyclizations were run using 2.5 equiv of BF_3·OEt_2, 2.5 equiv of aldehyde and 1.5 equiv of 2,6-di-*tert*-butylpyridine. [b] Product yields are after chromatography. [c] Diastereomeric ratios were based on isolated yields or ^{1}H NMR analysis. [d] 2.0 equiv of BF_3·OEt_2, 1.2 equiv of isobutyraldehyde and 1.2 equiv of 2,6-di-*tert*-butylpyridine were used.

cancer cells.[5] It has attracted the interest of a number of synthetic chemists, and the first total synthesis was recently reported by the Leighton group.[6,7] Our synthetic analysis identified aldehyde **17** and enol ether **21** as key building blocks that should undergo aldol−Prins coupling to produce most of the leucascandrolide A skeleton in a single step. The syntheses of **17** and **21** are illustrated in Scheme 1, and their coupling and ultimate conversion to the leucascandrolide A macrolide are outlined in Scheme 2.

Synthesis of the optically pure aldehyde **17** followed well-established methods. Noyori hydrogenation[8] of **14** introduced the first stereogenic center with 94% ee. Protection, reduction, and iodide formation gave the alkylating agent **15** in good yield. Myers' pseudoephedrine auxiliary[9] was used to introduce the C12 stereocenter by alkylation of iodide **15**, and acid treatment gave

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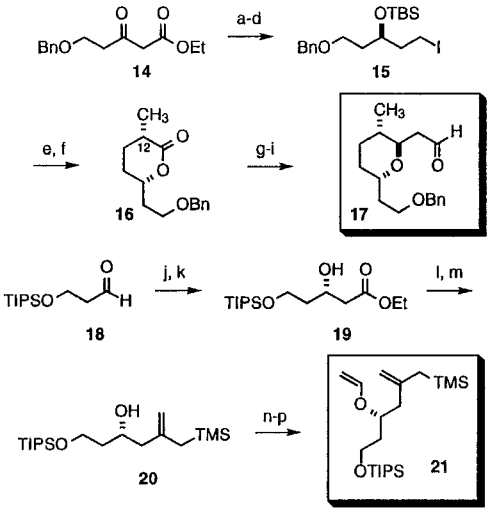
Scheme 1. Syntheses of the Aldol-Prins Precursors **17** and **21** of Leucascandrolide A[a]



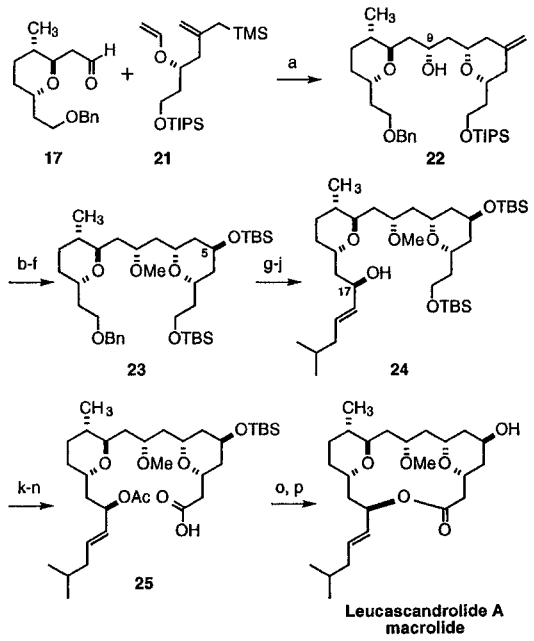
[a] (a) [(*R*)-BINAP]-RuCl(C_6H_6), 80 atm H_2, EtOH, 96%, 94% ee; (b) TBSCl, imidazole, DMF, 86%; (c) DIBALH, THF, −25 °C, 88%; (d) PPh_3, I_2, imidazole, CH_2Cl_2, quant.; (e) combine LDA, (−)-pseudoephedrine propionamide, LiCl, then add **15**, THF, −78 °C, 98%, ≥20:1 dr; (f) 2N H_2SO_4, dioxane, 95 °C, 77%; (g) *i.* DIBALH, CH_2Cl_2, −78 °C, *ii.* Ac_2O, DMAP, pyridine, 95%; (h) Allyltrimethylsilane, BF_3·OEt_2, CH_2Cl_2; −78 °C, 97%, ≥20:1 dr; (i) O_3, CH_2Cl_2, −78 °C, then PPh_3, 95%; (j) N_2CHCO_2Et, $SnCl_2$, CH_2Cl_2, 72%; (k) [(*S*)-BINAP]-RuCl(C_6H_6), 4 atm H_2, EtOH, 100 °C, 51%, ≥95% ee; (l) TMSCl, Et_3N, CH_2Cl_2, 91%; (m) *i.* $CeCl_3$, $TMSCH_2MgCl$, THF/Et_2O, −78 °C to 23 °C, *ii.* SiO_2 gel, CH_2Cl_2, 87% (n) $ClCH_2COCl$, pyridine, CH_2Cl_2, 95%; (o) i. DIBALH, CH_2Cl_2, −78 °C, *ii.* Ac_2O, DMAP, pyridine, 95%; (p) *Li*°, NH_3, THF, −78 °C, 65%.

the lactone **16** with ≥20:1 selectivity. Reductive acetylation,[10] axial allylation, and ozonolysis completed the synthesis of **17**.

The synthesis of **21** was also straightforward. Noyori hydrogenation of a β-keto ester generated the only stereogenic center in the target with >94% ee. Bunnelle's method[11] was used to convert the ester **19** to the 2-substituted allylsilane **20.** The sensitive enol ether was introduced using a new method: esterification with chloroacetyl chloride, reductive acetylation,[10] and elimination of the acetate and chloride groups by Li/NH_3 reduction. The enol ether **21** was isolated in good overall yield. We will continue to develop this promising new enol ether synthesis. With **17** and **21** in hand, the key aldol−Prins reaction could be investigated.

Aldehyde **17** and enol ether **21** were coupled using the same conditions described in Table 1, BF_3·OEt_2 and 2,6-*di-tert*-butylpyridine at −78 °C, to give the product **22** as a 5.5:1 mixture of epimers at C9 in 78% yield.[12,13] The major epimer was shown to have the desired (*S*)-configuration by advanced Mosher's analysis.[14] The problematic methylation of C9 was carried out with trimethyloxonium tetrafluoroborate and Proton Sponge, and the C9 epimers were separated at this stage. Oxidative cleavage of the alkene and L-Selectride reduction introduced the axial C5 alcohol, and reprotection gave **23**. The C17 substituent was

Scheme 2. Aldol−Prins Coupling and Synthesis of the Leucascandrolide A Macrolide[a]



[a] (a) i. BF_3·OEt_2, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, −78 °C, *ii.* $NaBH_4$, EtOH, 78%, 5.5:1 dr at C9; (b) $MeO^+BF_4^-$, Proton Sponge, 4 Å M.S., CH_2Cl_2, 79% (single epimer) plus C9 epimer (15%), (c) *i.* OsO_4, NMO, *ii.* $NaIO_4$, 80%; (d) L-Selectride, THF, −90 to −60 °C, 82% (single epimer) plus C5 epimer (10%); (e) TBAF, THF, 92%; (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, 89%; (g) H_2, $Pd(OH)_2$, EtOAc, 96%; (h) Swern, 94%; (i) Me_2AlCl, $Me_3SnCCCH_2CH(CH_3)_2$, $PhCH_3$, −78 °C, 80%, 3.5:1 dr at C17; (j) Red-Al, Et_2O, 60% (single epimer) plus recovered SM and C17 epimer; (k) Ac_2O, DMAP, pyridine, CH_2Cl_2, 89%; (l) Neutral Al_2O_3, hexanes, 96%; (m) Swern, 97%; (n) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, 71%; (o) *i.* K_2CO_3, MeOH, *ii.* $Cl_3C_6H_2COCl$, Et_3N, DMAP, C_6H_6, 23 °C, 56%; (p) HF·pyridine, THF, 96%.

introduced by a chelation-controlled alkynylstannane addition to the corresponding aldehyde.[15] The selectivity was 3.5:1, which is slightly higher than what Leighton found using a diastereoselective alkenylzinc addition.[6] Red-Al reduction gave the *(E)*-alkene **24**. The minor C17 epimer was easily separated at this stage. Reprotection and oxidation of the C1 alcohol gave the seco acid ester **25**. Hydrolysis, Yamaguchi-type cyclization,[16] and desilylation completed the synthesis of the leucascandrolide A macrolide. Synthetic leucascandrolide A macrolide showed ^1H and ^{13}C NMR data that was identical to that provided by Professor Leighton. The side chain of leucascandrolide A has been attached to the macrolide in two steps,[6] and thus our work constitutes a formal total synthesis of leucascandrolide A.

The aldol−Prins reaction brings together an aldehyde and an enol ether to form a new tetrahydropyran ring. The reaction is successful with a variety of aldehydes, and its utility can be seen in the synthesis of leucascandrolie A macrolide. We will continue to explore the selectivity and scope of this new method.

Acknowledgment. Financial support was by the National Institutes of Health (CA81635). Professor Lighton kindly provided ^1H and ^{13}C NMR spectra for the leucascandrolide macrolide.

Supporting Information Available: Experimental procedures and compound characterization for the work described (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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